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Bill J. Peck

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EXAMINER

CROW, ROBERT THOMAS

ART UNIT

PAPER NUMBER

1634

NOTIFICATION DATE

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ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IPOPS.LEGAL@agilent.com

Office Action Summary	Application No. 10/813,467	Applicant(s) PECK ET AL.	
	Examiner Robert T. Crow	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 January 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 28-43,45-47,49-59 and 61 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 28-43,45-47,49-59 and 61 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9 January 2009 has been entered.

Status of the Claims

2. This action is in response to papers filed 9 January 2009 in which claims 28, 45, 53 and 56 were amended, claims 44 and 48 were canceled, and no new claims were added. All of the amendments have been thoroughly reviewed and entered.

The previous rejections under 35 U.S.C. 103(a) not reiterated below are withdrawn in view of the amendments. Applicant's arguments have been thoroughly reviewed and are addressed following the rejections necessitated by the amendments.

Claims 28-43, 45-47, 49-59, and 61 are under prosecution.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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4. Claims 28-32, 34-43, 45-47, 49-50, 53-55, and 61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 28-32, 34-43, 45-47, 49-50, 53-55, and 61 are indefinite in claim 28, which recites the limitation "said surface of said substrate" in the penultimate line of claim 28. The recitation "said surface of said substrate" lacks proper antecedent basis in the recitation of "said entire surface of said substrate" in lines 3 and 9-10 of claim 28. It is suggested that the claim be amended to reflect proper antecedent basis.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

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consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 28-36, 38-43, 46-47, 49-52, 54-59, and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gamble et al (U.S. Patent No. 5,981,733, issued 9 November 1999) in view of Anderson et al (U.S. Patent No 5,186,824, issued 16 February 1993) in view of Bass et al (U.S. Patent Application Publication No. US 2003/0003222 A1, published 2 January 2003) in view of Schleifer et al (U.S. Patent No. 6,309,828, issued 30 October 2001) and, as applied to claim 34, as evidenced by the online dictionary at Merriam-webster.com.

Regarding claim 28, Gamble et al teach a method of synthesizing an addressable array of nucleic acid molecules on a substrate. Gamble et al teach a substrate upon which micro-sized spots of reagents are dispensed in particular locations (column 3, lines 35-45). The reagents are removable from the substrate surface (column 2, lines 45-50), and thus are attached to the surface. The reagents are phosphoramidites (column 2, lines 13-16), which are blocked nucleoside monomers in accordance with the example presented in the first paragraph on page 15 of the instant specification. Thus, the claim has been given the broadest reasonable interpretation consistent with the teachings of the specification regarding a "blocked nucleoside monomer" (*In re Hyatt*, 211 F.3d1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000) (see MPEP 2111 [R-1])). Because the spotted blocked nucleoside monomers are localized onto specific locations on the substrate (column 2, lines 15-25), and because

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the locations are predetermined by a user prior to synthesis of the array (column 2, lines 39-45), the array is an addressable array in accordance with the example presented on page 10 of the instant specification. Thus, the claim has been given the broadest reasonable interpretation consistent with the teachings of the specification regarding an "addressable array."

Gamble et al teach additional reagents are transported to a reaction chamber which contacts the substrate, wherein the additional reagents include deprotecting reagents (column 4, lines 35-45). The deprotecting reagent is a deblocking agent in a fluid because it removes a trityl protecting group that blocks further synthesis on the nucleoside monomer (column 12, lines 59-67).

Gamble et al also teach the deblocking fluid is then displaced from the surface of the substrate, which now comprises attached unblocked nucleoside monomers, using a purging fluid in the form of a wash fluid used between synthesis steps (column 10, lines 15-25). Gamble et al also teach the attached unblocked nucleoside on the surface is then reacted with another blocked nucleoside monomer to produce the addressable array of nucleic acid molecules on the surface; namely, the next blocked phosphoramidite molecule is applied to the substrate after the substrate is oriented with away from the reaction chamber and towards a jetting system that jets a phosphoramidite at selected loci (i.e., on the array (column 15, line 50-column 16, line 5 and column 3, lines 35-45).

While Gamble et al teach the substrate is placed in a reaction chamber wherein reagents flow over and immerse the substrate (column 3, line 45-column 4, line 5), and

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that the reagents include phosphoramidites (i.e., blocked nucleoside monomers), wash reagents, deprotection (i.e. deblocking) reagents, activation reagents, oxidation reagents, and any other necessary synthesis reagents (column 4, lines 35-46), Gamble et al do not explicitly teach the wash reagent contact said entire surface of the substrate; i.e., that the wash solution flows through the same chamber in a manner sufficient to produces a stratified fluid interface.

However, Anderson et al teach a method for producing an array of oligonucleotides on a substrate, wherein a first nucleoside capped with a trityl group attached to the surface of a support (i.e., substrate; column 19, line 40-column 20, line 50), followed by detritylation of the nucleotide with a blocking fluid; namely, step i of Table I (column 20), which generates an unblocked attached nucleoside nucleotide. Anderson et al teach displacing the deblocking fluid with a purging fluid; namely, a surface of the substrate (i.e., solid support) is exposed to reagents sequentially wherein the reagents are kept separate based on density (column 5, lines 3-38 and column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface, wherein interface 124, which is indicative of the stratified layers, is formed during the method (column 12, lines 28-67 and Fig. 2A-2D). Thus, the wash solution flows through the same chamber in a manner sufficient to produces a stratified fluid interface, and flows across the surface of the substrate. Anderson et al also teach the reacting of the unblocked attached nucleotide with another blocked nucleoside monomer; namely, coupling step ii of Table I (column 20). Anderson et al also teach increased washing efficiency and quantitative replacement of one reagent by the next is

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a fixed requirement for polymer synthesis on a surface (column 19, lines 25-40), and that extensive washing between use of reagents is necessary to ensure each reagent reacts properly so that the yield of the polymer is not diminished (column 3, lines 45-60). Anderson et al also teach the use of a single hollow chamber as a reaction chamber has the added advantage of allowing precise control of fluid flow and minimization of both micro-and macro-anomalous flow (Abstract). Thus, Anderson et al teach the known technique of performing all of the fluid steps, including washing, with a single reaction chamber wherein the fluids flow across the surface of the substrate.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising steps including washing of the array substrate as taught by Gamble et al so that each previous reagent is quantitatively replaced by a washing fluid in a manner sufficient to produce a stratified fluid interface that moves across the surface of the substrate as taught by Anderson et al and so that the reaction chamber of Gamble et al is used as a single reaction chamber for all of the fluid manipulation steps as taught by Anderson et al arrive at the instantly claimed method with a reasonable expectation of success. Quantitative replacement of reagents on the surface of the support requires displacement of said reagent from the entire surface of the substrate via use of the washing fluid as taught by Anderson et al. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method having the added advantage of ensuring that each reagent reacts properly so that the yield of the polymer is not diminished, thus meeting the fixed requirements of

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washing efficiency and quantitative replacement of solutions during polymer synthesis as explicitly taught by Anderson et al (column 19, lines 25-40 and column 3, lines 45-60). The ordinary artisan would also have been motivated to use the single reaction chamber of Anderson et al as a single reaction chamber for all of the fluid steps in the method of Gamble et al because the use of a single reaction chamber for all of the fluid steps, including washing, would have resulted in a method having the additional added advantage of allowing precise control of fluid flow and minimization of both micro-and macro-anomalous flow as explicitly taught by Anderson et al (Abstract). In addition, it would have been obvious to a person of ordinary skill in that art at the time the claimed invention was made that the known technique of performing all of the fluid steps, including washing, with a single reaction chamber as taught by Anderson et al could have been applied to the method of Gamble et al with predictably results because the known technique of performing all of the fluid steps, including washing, with a single reaction chamber as taught by Anderson et al predictably results in a reliable method of performing DNA synthesis steps.

Gamble et al teach the fluids enter and exit reaction chamber 26 in through the fluid inlet 32 and out through fluid outlet 34 (i.e., ports 32 and 34; Figures 4a-c and column 5, lines 55-65). Thus, the fluids move across the surface of the substrate. Anderson et al also teach the synthesis steps are done on a substrate (i.e., a flat disk; column 6, lines 49-60) in a flow cell in the form of a chamber (Figure 1 and Abstract), which comprises a lower fluid inlet in the form of the opening of fluid line 100 and an

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upper fluid outlet in the form of the opening of fluid line 102 (Figure 1 and column 12, lines 20-30). Thus, the fluids move across the surface of the substrate.

Thus, while Gamble et al and Anderson et al both teach fluid inlets and outlets that allow the flow of fluids across the surface of the substrate, and while Anderson et al teach the synthesis is done in the flow cell (i.e., the chamber of Figure 1), the references do not explicitly teach the jetted substrate of Gamble et al is placed within a flow cell for the displacing step and that the entire substrate is contacted with fluids..

However, Bass et al teach the manufacturing of biopolymer arrays (Abstract), wherein nucleotide monomers are jetted on a substrate, followed by placement of the substrate into a flow cell having a fluid inlet and a fluid outlet, and wherein purging fluids in the form of washing fluids are added to the substrate within the flow cell from the left input side and flow out through the right outlet side (paragraph 0051 and Figure 1). Thus, the fluids move across the surface of the substrate. Bass et al teach the reactions are performed by treating the entire substrate by flooding with the appropriate reagent (paragraphs 0035-0037), which is in accordance with the embodiment described on page 17 of the instant specification for contacting the entire substrate with a fluid. Thus, the claim has been given the broadest reasonable interpretation consistent with the teachings of the specification regarding "contacting said entire surface of said substrate." Bass et al also teach the use of the flow cell for the synthesis steps has the added advantage of allowing the determination of the level of contaminants in the fluids exiting the flow cells (paragraph 0047). Thus, Bass et al

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teach the known technique of placing a jetted substrate within a flow cell for the displacing (i.e., purging) step.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising the use of flow cells comprising inlets and outlets as taught by Gamble et al in view of Anderson et al so that the jetted substrate is placed within a flow cell for the displacing (i.e., purging) step as taught by Bass et al. The modification would result in the stratified fluid interface of Gamble et al in view of Anderson et al moving across the surface of the substrate, thus arriving at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method having the added advantage of allowing determination of the level of contaminants in the fluids exiting the flow cells as explicitly taught by Bass et al (paragraph 0047). In addition, it would have been obvious to the ordinary artisan that the known technique of jetted substrate within a flow cell for the displacing step as taught by Bass et al could have been applied to the method of Gamble et al in view of Anderson et al with predictable results because the known technique of jetted substrate within a flow cell for the displacing step as taught by Bass et al predictably results in the reliable synthesis of oligonucleotides on a substrate surface.

Neither Gamble et al, Anderson et al, nor Bass et al explicitly teach the oligonucleotides are covalently bonded to the substrate.

However, Schleifer et al teach a method of polymer synthesis comprising repeated monomer additions to supports, cleavage of the polymers from the supports and immobilization of the polymers to feature locations on the array (column 9, lines 22-column 10, line 30 and Example 3) whereby an addressable array is produced (see definition of array, column 1, lines 13-15). Schleifer et al also teach the deposition of the molecules onto the substrate utilizes covalent coupling of activated oligonucleotides with solid supports (column 9, lines 1-20), which is an efficient, cost-effective method of spatially integrating polymer synthesis and replicate array fabrication (Abstract, column 2, lines 22-31). Thus, Schleifer et al teach the known technique of covalently linking oligonucleotides to a substrate at a plurality of addressable features.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Gamble et al in view of Anderson et al and Bass et al so that the an addressable array comprises oligonucleotides covalently bound to the substrate at the plurality of addressable features as taught by Schleifer et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method having the added advantage of utilizing an efficient, cost-effective method of spatially integrating polymer synthesis and replicate array fabrication as explicitly taught by Schleifer et al (Abstract, column 2, lines 22-31). In addition, it would have been obvious to the ordinary artisan that the known technique of covalently linking the oligonucleotides as taught by Schleifer et al could have been applied to the method of Gamble et al in view of

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Anderson et al and Bass et al with predictable results because the known technique of covalently linking the oligonucleotides as taught by Schleifer et al predictably results in the reliable attachment of oligonucleotides to a substrate surface.

Regarding claim 29, the method of claim 28 is discussed above. Anderson et al also teach a blocked nucleoside monomer is attached to the substrate by contacting the substrate with a fluid comprising a blocked nucleoside monomer at a location on the substrate that comprises hydroxy groups; namely, Anderson et al teach a general method for oligonucleotide synthesis, wherein the blocked monomer in step ii of Table I is added to the unblocked attached nucleotide of step i, which has a free hydroxyl group at the 5' end generated by the detritylation step (column 19, line 40-column 20, line 50).

Therefore, it would have been obvious to the ordinary artisan at the time the claimed invention was made that the known general method of oligonucleotide synthesis of Anderson et al comprising the use of tritylated phosphoramidite monomer groups, deblocking fluids, and wash fluids of Anderson et al could have been applied in place of the synthesis method of Gamble et al in view of Anderson et al, Bass et al and Schleifer et al, which also comprises the use of tritylated phosphoramidite monomer groups (column 2, lines 25-35), deblocking fluids, and wash fluids, with predictable results because the known general method of oligonucleotide synthesis of Anderson et al predictably results in the reliable synthesis of oligonucleotides on a solid support.

Regarding claim 30, the method of claim 28 is discussed above. Gamble et al teach the steps of the method are repeated a plurality of times; namely, the method synthesizes polymers (column 2, lines 39-47) of nucleotides (column 2, lines 13-16).

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Because oligonucleotide polymers have multiple nucleotides therein, the steps are repeated a plurality of times. Alternatively, Anderson et al also teach the steps are repeated a plurality of times (column 20, lines 2). Thus, modification of the method of Gamble et al in view of Bass et al and Schleifer et al with the teachings of Anderson et al results in a method wherein the steps of the method are repeated a plurality of times.

Regarding claim 31, the method of claim 28 is discussed above. Gamble et al teach the substrate comprises a surface of a planar support; namely, the support is a microscope slide (column 3, lines 5-10 and substrate 20 of Figure 1), which is planar because it is flat.

Alternatively, Anderson et al also teach the substrate comprises a surface of a planar support; namely, the support is a flat disc (column 6, lines 49-56). Thus, modification of the method of Gamble et al in view of Bass et al and Schleifer et al with the teachings of Anderson et al a results in a method wherein the substrate comprises a surface of a planar support.

In addition, Bass et al teach the use of planar supports in the form of flat substrates (paragraph 0019). Thus, modification of the method of Gamble et al in view of Anderson et al and Schleifer et al with the teachings of Bass et al a results in a method wherein the substrate comprises a surface of a planar support.

Regarding claim 32, the method of claim 28 is discussed above. Anderson et al also teach the displacing step causes minimal mixing of deblocking and purging fluids; namely, density differences are used to minimize mixing (column 10, lines 23-24). Thus, modification of the method of Gamble et al in view of Bass et al and Schleifer et al with

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the teachings of Anderson et al a results in a method wherein the displacing step causes minimal mixing of deblocking and purging fluids.

Regarding claim 34, the method of claim 28 is discussed above. Gamble et al also teach the substrate comprises a surface of a planar support; namely, the support is a microscope slide (column 3, lines 5-10 and substrate 20 of Figure 1), which is planar because it is flat. The surface is nascent because the surface is activated before synthesis (column 15, lines 50-55). Because the specification has no limiting definition of the word "nascent," the word is interpreted as "having recently come into existence" in accordance with the online dictionary at Merriam-webster.com. Thus, modification of the method of Gamble et al in view of Bass et al and Schleifer et al with the teachings of Anderson et al a results in a method wherein the substrate comprises a nascent surface of a planar support

Regarding claim 35, the method of claim 28 is discussed above. Anderson et al also teach the purging fluid has a density that is different from the deblocking fluid; namely, the solid supports are exposed to reagents sequentially wherein the reagents are kept separate based on density (Column 5, lines 3-38 and Column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (Column 12, lines 28-67 and Fig. 2A-2D). Thus, modification of the method of Gamble et al in view of Bass et al and Schleifer et al with the teachings of Anderson et al results in a method wherein the purging fluid has a density that is different from the deblocking fluid.

Regarding claims 36 and 38, the method of claim 28 is discussed above.

Anderson et al also teach the deblocking fluid and the purging fluid have a density difference, expressed as the Atwood number, of 0.01 or more. In a single exemplary embodiment, Anderson et al teach the deblocking (detritylation) fluid has a density that is greater than that of methylene chloride (i.e., 1.325 g/mL; column 21, lines 1-10).

Detritylation is followed with a wash using acetonitrile as a purging solution, which has a density of 0.714 g/mL (Table II, step 3). Calculating the density difference using pure methyl chloride results in an Atwood number of 0.2996; a higher density deblocking fluid gives a higher Atwood number. Thus, modification of the method of Gamble et al in view of Bass et al and Schleifer et al with the teachings of Anderson et al results in a method wherein the deblocking fluid and the purging fluid have a density difference, expressed as the Atwood number, of 0.01 or more.

Regarding claim 39, the method of claim 28 is discussed above. Anderson et al also teach the purging fluid is an organic fluid; namely, 50% dichloromethane and 50% dimethylformamide (Table II). Thus, modification of the method of Gamble et al in view of Bass et al and Schleifer et al with the teachings of Anderson et al results in a method wherein the purging fluid is an organic fluid.

Regarding claim 40, the method of claim 28 is discussed above. Anderson et al also teach the purging fluid comprises an oxidizing agent; namely, the purging fluid is interpreted to be all of the fluids of Table I following the deprotection step i (column 20), which are introduced in one long series of changing densities (column 7, lines 5-19). The series that makes up the purging fluid includes the oxidizing agent iodine (step iv of

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Table I). Thus, modification of the method of Gamble et al in view of Bass et al and Schleifer et al with the teachings of Anderson et al results in a method wherein the purging fluid comprises an oxidizing agent.

Regarding claims 41 and 42, the method of claim 28 is discussed above.

Anderson et al also teach the purging fluid comprises a wash fluid; namely, step 3 of Table II is a washing step using 50% dichloromethane and 50% dimethylformamide (i.e., claim 17; Table II), which is an organic fluid (i.e., claim 18). Thus, modification of the method of Gamble et al in view of Bass et al and Schleifer et al with the teachings of Anderson et al results in a method wherein the purging fluid comprises a wash fluid.

Regarding claim 43, the method of claim 41 is discussed above. Anderson et al also teach the wash fluid is acetonitrile (column 13, line 67-column 14, line 1). Thus, modification of the method of Gamble et al in view of Bass et al and Schleifer et al with the teachings of Anderson et al results in a method wherein the wash fluid is acetonitrile.

Regarding claim 46, the method of claim 28 is discussed above. Anderson et al also teach the purging fluid limits the efficiency of the deblocking fluid; namely, the deblocking reaction requires acid (e.g., dichloroacetic acid; step i of Table I). Addition of any washing fluid decreases the concentration of acid, thereby limiting the efficiency of deblocking. Thus, modification of the method of Gamble et al in view of Bass et al and Schleifer et al with the teachings of Anderson et al results in a method wherein the purging fluid limits the efficiency of the deblocking fluid.

Regarding claim 47, the method of claim 29 is discussed above. Anderson et al also teach the hydroxyl groups are 5' OH groups of nucleoside polymers deblocked by the detritylation step (column 19, line 40-column 20, line 50). Thus, modification of the method of Gamble et al in view of Bass et al and Schleifer et al with the teachings of Anderson et al results in a method wherein the hydroxyl groups are 5' OH groups of nucleoside polymers deblocked by the detritylation step

Regarding claim 49, the method of claim 29 is discussed above. Gamble et al teach the block nucleoside monomer is deposited at the location by pulse jetting; namely, micro-sized spots of reagents are dispensed in particular locations (column 3, lines 35-45) by pulse jetting (column 9, lines 50-65).

Regarding claim 50, the method of claim 28 is discussed above. Gamble et al teach the blocking group is a trityl group (column 2, lines 25-35), which is an acid labile group. In addition, Anderson et al also teach the blocking group is a trityl group (column 19, line 40-column 20, line 50), which is an acid labile group, and the deblocking fluid comprises dichloroacetic acid (step i of Table I). Thus, modification of the method of Gamble et al in view of Bass et al and Schleifer et al with the teachings of Anderson et al results in a method wherein the blocking group is a trityl group which is deblocked with an acid.

Regarding claim 54, the method of claim 28 is discussed above. Anderson et al also teach the deblocking fluid comprises an organic solvent; namely, acetonitrile (column 13, line 67-column 14, line 1). The vapor pressure of acetonitrile at 0°C and 1 ATM pressure is 24.75 mm Hg, which is 3.3 kPa. Thus, modification of the method of

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Gamble et al in view of Bass et al and Schleifer et al with the teachings of Anderson et al results in a method wherein the deblocking fluid comprises an organic solvent having the required vapor pressure.

Regarding claim 55, the method of claim 28 is discussed above. Anderson et al also teach contacting the substrate comprising the attached blocked nucleoside polymer with an oxidation fluid prior to contacting with the deblocking fluid; namely, oxidation of an added nucleoside is performed before the sequential addition of the next monomer (Table I, step iv). Thus, modification of the method of Gamble et al in view of Bass et al and Schleifer et al with the teachings of Anderson et al results in a method wherein the substrate comprising the attached blocked nucleoside polymer is contacted with an oxidation fluid prior to contacting with the deblocking fluid.

Regarding claim 56, Gamble et al teach a method of synthesizing an addressable array of at least two oligonucleotides bonded to different known locations on a substrate. Gamble et al teach a substrate upon which micro-sized spots of reagents are dispensed in particular locations (i.e., first and second locations; column 3, lines 35-45); thus, there are at least two oligonucleotides bonded at different locations. The reagents are removable from the substrate surface (column 2, lines 45-50), and thus are attached to the surface. The reagents are phosphoramidites (column 2, lines 13-16), which are blocked nucleoside monomers in accordance with the example presented in the first paragraph on page 15 of the instant specification. Thus, the claim has been given the broadest reasonable interpretation consistent with the teachings of the specification regarding a "blocked nucleoside monomer." Because the spotted

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blocked nucleoside monomers are localized onto specific locations on the substrate (column 2, lines 15-25), and because the locations are predetermined by a used prior to synthesis of the array (column 2, lines 39-45), the array is an addressable array in accordance with the example presented on page 10 of the instant specification. Thus, the claim has been given the broadest reasonable interpretation consistent with the teachings of the specification regarding an "addressable array." The monomers are deblocked by deprotecting reagents to remove a trityl protecting group that blocks further synthesis on the nucleoside monomer (column 4, lines 35-45 and column 12, lines 59-67). The deblocking unmask functional groups on the attached unblocked nucleoside on the surface which are then reacted with another blocked nucleoside monomer to produce the addressable array of nucleic acid molecules on the surface; namely, the next blocked phosphoramidite molecule is applied (column 13, lines 15-30).

Gamble et al teach additional reagents are transported to a reaction chamber which contacts the substrate, wherein the additional reagents include deprotecting reagents (column 4, lines 35-45). The deprotecting reagent is a deblocking agent because it removes a trityl protecting group that blocks further synthesis on the nucleoside monomer (column 12, lines 59-67). The monomers are therefore unblocked. The deblocking fluid is then displaced from the surface of the substrate using a purging fluid in the form of a wash fluid used between synthesis steps (column 10, lines 15-25). The unblocked monomers are then reacted with another blocked nucleotide monomer to produce the array having a first oligonucleotide at the first location and the second oligonucleotide at the second location; namely, the next blocked phosphoramidite

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molecule is applied to the substrate after the substrate is oriented with away from the reaction chamber and towards a jetting system that jets a phosphoramidite at selected loci (i.e., on the array (column 15, line 50-column 16, line 5 and column 3, lines 35-45).

While Gamble et al teach the surface is contained within a reaction chamber wherein reagents flow over and immerse the substrate (column 3, line 45-column 4, line 5), and that the reagents include phosphoramidites (i.e., blocked nucleoside monomers), wash reagents, deprotection (i.e. deblocking) reagents, activation reagents, oxidation reagents, and any other necessary synthesis reagents (column 4, lines 35-46), Gamble et al do not explicitly teach the wash reagent contacts the entire surface of the substrate; i.e., that the wash solution flows through the same chamber in a manner sufficient to produces a stratified fluid interface.

However, Anderson et al teach a method for producing an array of oligonucleotides on a substrate, wherein a first nucleoside capped with a trityl group attached to the surface of a support (i.e., substrate; column 19, line 40-column 20, line 50), followed by detritylation of the nucleotide with a blocking fluid; namely, step i of Table I (column 20), which generates an unblocked attached nucleoside nucleotide. Anderson et al teach displacing the deblocking fluid with a purging fluid; namely, a surface of the substrate (i.e., solid support) is exposed to reagents sequentially wherein the reagents are kept separate based on density (column 5, lines 3-38 and column 6, lines 13-36) forming a liquid-liquid interface such that the solid support is not exposed to a triple phase interface, wherein interface 124, which is indicative of the stratified layers, is formed during the method (column 12, lines 28-67 and Fig. 2A-2D). Thus, the wash

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solution flows through the same chamber in a manner sufficient to produces a stratified fluid interface, and flows across the surface of the substrate. Anderson et al also teach the reacting of the unblocked attached nucleotide with another blocked nucleoside monomer; namely, coupling step ii of Table I (column 20). Anderson et al also teach increased washing efficiency and quantitative replacement of one reagent by the next is a fixed requirement for polymer synthesis on a surface (column 19, lines 25-40), and that extensive washing between use of reagents is necessary to ensure each reagent reacts properly so that the yield of the polymer is not diminished (column 3, lines 45-60). Anderson et al also teach the use of a single hollow chamber as a reaction chamber has the added advantage of allowing precise control of fluid flow and minimization of both micro-and macro-anomalous flow (Abstract). Thus, Anderson et al teach the known technique of performing all of the fluid steps, including washing, with a single reaction chamber wherein the fluids flow across the surface of the substrate.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising steps including washing of the array substrate as taught by Gamble et al so that each previous reagent is quantitatively replaced by a washing fluid in a manner sufficient to produce a stratified fluid interface that moves across the surface of the substrate as taught by Anderson et al and so that the reaction chamber of Gamble et al is used as a single reaction chamber for all of the fluid manipulation steps as taught by Anderson et al arrive at the instantly claimed method with a reasonable expectation of success. Quantitative replacement of reagents on the surface of the support requires

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displacement of said reagent from the entire surface of the substrate via use of the washing fluid as taught by Anderson et al. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method having the added advantage of ensuring that each reagent reacts properly so that the yield of the polymer is not diminished, thus meeting the fixed requirements of washing efficiency and quantitative replacement of solutions during polymer synthesis as explicitly taught by Anderson et al (column 19, lines 25-40 and column 3, lines 45-60). The ordinary artisan would also have been motivated to use the single reaction chamber of Anderson et al as a single reaction chamber for all of the fluid steps in the method of Gamble et al because the use of a single reaction chamber for all of the fluid steps, including washing, would have resulted in a method having the additional added advantage of allowing precise control of fluid flow and minimization of both micro-and macro-anomalous flow as explicitly taught by Anderson et al (Abstract). In addition, it would have been obvious to a person of ordinary skill in that art at the time the claimed invention was made that the known technique of performing all of the fluid steps, including washing, with a single reaction chamber as taught by Anderson et al could have been applied to the method of Gamble et al with predictably results because the known technique of performing all of the fluid steps, including washing, with a single reaction chamber as taught by Anderson et al predictably results in a reliable method of performing DNA synthesis steps.

Gamble et al teach the fluids enter and exit reaction chamber 26 in through the fluid inlet 32 and out through fluid outlet 34 (i.e., ports 32 and 34; Figures 4a-c and

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column 5, lines 55-65). Thus, the fluids move across the surface of the substrate.

Anderson et al also teach the synthesis steps are done on a substrate (i.e., a flat disk; column 6, lines 49-60) in a flow cell in the form of a chamber (Figure 1 and Abstract), which comprises a lower fluid inlet in the form of the opening of fluid line 100 and an upper fluid outlet in the form of the opening of fluid line 102 (Figure 1 and column 12, lines 20-30). Thus, the fluids move across the surface of the substrate.

Thus, while Gamble et al and Anderson et al both teach fluid inlets and outlets that allow the flow of fluids across the surface of the substrate, and while Anderson et al teach the synthesis is done in the flow cell (i.e., the chamber of Figure 1), the references do not explicitly teach the jetted substrate of Gamble et al is placed within a flow cell for the displacing step.

However, Bass et al teach the manufacturing of biopolymer arrays (Abstract), wherein nucleotide monomers are jetted on a substrate, followed by placement of the substrate into a flow cell having a fluid inlet and a fluid outlet, and wherein purging fluids in the form of washing fluids are added to the substrate within the flow cell from the left input side and flow out through the right outlet side (paragraph 0051 and Figure 1).

Thus, the fluids move across the surface of the substrate. Bass et al teach the reactions are performed by treating the entire substrate by flooding with the appropriate reagent (paragraphs 0035-0037), which is in accordance with the embodiment described on page 17 of the instant specification for contacting the entire substrate with a fluid. Thus, the claim has been given the broadest reasonable interpretation consistent with the teachings of the specification regarding "contacting said entire

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surface of said substrate.” Bass et al also teach the use of the flow cell for the synthesis steps has the added advantage of allowing the determination of the level of contaminants in the fluids exiting the flow cells (paragraph 0047). Thus, Bass et al teach the known technique of placing a jetted substrate within a flow cell for the displacing (i.e., purging) step.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising the use of flow cells comprising inlets and outlets as taught by Gamble et al in view of Anderson et al so that the jetted substrate is placed within a flow cell for the displacing (i.e., purging) step as taught by Bass et al. The modification would result in the stratified fluid interface of Gamble et al in view of Anderson et al moving across the surface of the substrate, thus arriving at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method having the added advantage of allowing determination of the level of contaminants in the fluids exiting the flow cells as explicitly taught by Bass et al (paragraph 0047). In addition, it would have been obvious to the ordinary artisan that the known technique of jetted substrate within a flow cell for the displacing step as taught by Bass et al could have been applied to the method of Gamble et al in view of Anderson et al with predictable results because the known technique of jetted substrate within a flow cell for the displacing step as taught by Bass et al predictably results in the reliable synthesis of oligonucleotides on a substrate surface.

Neither Gamble et al, Anderson et al, nor Bass et al explicitly teach the oligonucleotides are covalently bonded to the substrate.

However, Schleifer et al teach a method of polymer synthesis comprising repeated monomer additions to supports, cleavage of the polymers from the supports and immobilization of the polymers to feature locations on the array (column 9, lines 22-column 10, line 30 and Example 3) whereby an addressable array is produced (see definition of array, column 1, lines 13-15). Schleifer et al also teach the deposition of the molecules onto the substrate utilizes covalent coupling of activated oligonucleotides with solid supports (column 9, lines 1-20), which is an efficient, cost-effective method of spatially integrating polymer synthesis and replicate array fabrication (Abstract, column 2, lines 22-31). Thus, Schleifer et al teach the known technique of covalently linking oligonucleotides to a substrate at a plurality of addressable features.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Gamble et al in view of Anderson et al and Bass et al so that the an addressable array comprises oligonucleotides covalently bound to the substrate at the plurality of addressable features as taught by Schleifer et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method having the added advantage of utilizing an efficient, cost-effective method of spatially integrating polymer synthesis and replicate array fabrication as explicitly taught by Schleifer et al (Abstract, column 2, lines 22-31). In addition, it would have been obvious to the ordinary artisan

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that the known technique of covalently linking the oligonucleotides as taught by Schleifer et al could have been applied to the method of Gamble et al in view of Anderson et al and Bass et al with predictable results because the known technique of covalently linking the oligonucleotides as taught by Schleifer et al predictably results in the reliable attachment of oligonucleotides to a substrate surface.

Regarding claim 33, the method of claim 56 is discussed above. Gamble et al teach the substrate comprises a surface of a support containable within a flow cell; namely, the substrate is a slide (column 3, lines 5-10 and substrate 20 of Figure 1), which is capable of being contained within a flow cell.

Alternatively, Anderson et al also teach the substrate comprises a surface of a support containable within a flow cell; namely, the substrate (i.e., reaction media) is in the internal space of a hollow enclosure (column 5, lines 20-38), which is a flow cell. A review of the specification yields no limiting definition of a "flow cell;" thus, the claim has been given the broadest reasonable interpretation consistent with the teachings of the specification regarding a "flow cell." Thus, modification of the method of Gamble et al in view of Bass et al and Schleifer et al with the teachings of Anderson et al results in a method wherein the substrate comprises a surface of a support containable within a flow cell.

Further, Bass et al also teach the support is in the flow cell (paragraph 0059). Therefore, modification of the method of Gamble et al in view of Anderson et al and Schleifer et al with the teachings of Bass et al results in a surface of a support containable within a flow cell.

Finally, it is noted that while the support is required to be containable within a flow cell, the claim does not require an active method step wherein the substrate is actually placed within a flow cell.

Regarding claim 51, the method of claim 33 is discussed above. Gamble et al teach the fluids enter and exit reaction chamber 26 through the fluid inlet and fluid outlet (i.e., ports 32 and 34; Figures 4a-c and column 5, lines 55-65). Anderson et al also teach the synthesis steps are done on a substrate (i.e., a flat disk; column 6, lines 49-60) in a flow cell in the form of a rotor chamber (Figure 1 and Abstract), which comprises a fluid inlet in the form of the opening of fluid line 100 and a fluid outlet in the form of the opening of fluid line 102 (Figure 1 and column 12, lines 20-30). Finally, Bass et al teach the fluid enters the flow cell 100 from the left input side and flows out through the right outlet side (paragraph 0051 and Figure 1). Thus, modification of the method of Gamble et al in view of Anderson et al, Bass et al, and Schleifer et al results in use of a flow cell having a chamber with at least one fluid inlet and at least one fluid outlet.

Regarding claim 52, the method of claim 51 is discussed above. Gamble et al teach reaction chamber 26, which is a flow cell because fluids flow through it, that is oriented vertically (Figure 5).

Further, Anderson et al teach the flow cell (i.e., rotor) is oriented vertically (Abstract). Therefore, modification of the method of Gamble et al in view of Bass et al and Schleifer et al with the teachings of Anderson et al results in a vertically oriented flow cell.

In addition, Bass et al also teach the support is introduced into the flow cell vertically (paragraph 0059); thus, the flow cell has at least one portion oriented vertically. Therefore, modification of the method of Gamble et al in view of Anderson et al and Schleifer et al with the teachings of Bass et al results in a vertically oriented flow cell.

Regarding claim 57, the method of claim 56 is discussed above. Gamble et al teach the at least two oligonucleotides comprise the same sequence; namely, the method produces an array (Abstract) of oligonucleotides (column 2, lines 35-50) by jetting the reagents used to make the array (Abstract). Because Gamble teach each jet of a plurality of jets has the same reagent sent to it (column 6, lines 10-15), each jetted position comprises the same sequences.

In addition, Anderson et al also teach the at least two oligonucleotides comprise the same sequence; namely, the solutions are added to the support in a chamber (i.e., rotor; column 20, lines 55-65), which is interpreted as a single synthesis on a single support, thereby producing one full length sequence at more than one location on the support. Thus, modification of the method of Gamble et al in view of Bass et al and Schleifer et al with the teachings of Anderson et al results in a method wherein the at least two oligonucleotide comprise the same sequence composition.

Regarding claim 58, the method of claim 56 is discussed above. Gamble et al also teach the at least two oligonucleotides comprise the different sequence compositions; namely, the method produces an array (Abstract), wherein the arrays

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provide a large number of different compounds in a small space (column 1, lines 1-10), and the compounds are different oligonucleotides (column 2, lines 35-50).

Regarding claim 59, the method of claim 56 is discussed above. While neither Gamble et al, Anderson et al, Bass et al, nor Schleifer et al explicitly teach oxidation before deblocking, the courts have held that selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results (*In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946). See MPEP 2144.04 IV.C.

Regarding claim 61, the method of claim 28 is discussed above. Gamble et al teach the substrate is planar; namely, the support is a microscope slide (column 3, lines 5-10 and substrate 20 of Figure 1), which is planar because it is flat.

Alternatively, Anderson et al also teach the substrate comprises is planar; namely, the support is a flat disc (column 6, lines 49-56). Thus, modification of the method of Gamble et al in view of Bass et al and Schleifer et al with the teachings of Anderson et al a results in a method wherein the substrate is planar.

In addition, Bass et al teach the use of planar supports in the form of flat substrates (paragraph 0019). Thus, modification of the method of Gamble et al in view of Anderson et al and Schleifer et al with the teachings of Bass et al a results in a method wherein the substrate is planar.

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8. Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gamble et al (U.S. Patent No. 5,981,733, issued 9 November 1999) in view of Anderson et al (U.S. Patent No 5,186,824, issued 16 February 1993) in view of Bass et al (U.S. Patent Application Publication No. US 2003/0003222 A1, published 2 January 2003) in view of Schleifer et al (U.S. Patent No. 6,309,828, issued 30 October 2001) as applied to claim 28 above, and further in view of Greene et al (*Protective Groups in Organic Synthesis*, 3rd ed., Wiley and Sons, New York, 1999, page 106).

Regarding claim 37, the method of claim 28 is discussed above in Section 7.

Neither Gamble et al, Anderson et al, Bass et al, nor Schleifer et al explicitly teach the purging fluid density is higher than the deblocking fluid density.

However, Green et al teach the deblocking (i.e., cleavage) of dimethoxytrityl (i.e., trityl) groups of deoxyribonucleotides using 3% trichloroacetic acid (density 1.62 g/mL) in 95:5 nitromethane/methanol (densities 1.127 and 0.791 g/mL, respectively), with the added advantage that the mixture reduces the levels of depurination of the reaction product (page 106). Depurination results in a degraded product on the array.

It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to “prove that subject matter shown to be in the prior art does not possess characteristic relied on” (205 USPQ 594, second column, first full paragraph). In the instant case, the solvent mixture is predominantly nitromethane, with a density of 1.127 g/mL, with 5%

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methanol, having a lower density. A final concentration of 3% of the higher density trichloroacetic acid is believed to produce a solution with an overall density nearly equal to that of nitro methane, because similar percentages of both a higher density liquid and a lower density liquid are added. Thus, the final density of the solution of Greene et al is believed to be lower than 1.325 g/mL, which is the density of the purging fluid of Anderson et al. Thus, Greene et al teach the known technique of having a purging fluid density that is higher than the deblocking fluid density.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method as taught by Gamble et al in view of Anderson et al, Bass et al, and Schleifer et al so that the deblocking solution is the deblocking solution of lower density as taught by Greene et al to arrive at the instantly claimed invention with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method of producing an addressable array having the added advantage of having fewer degraded products on the array via a reduction in the levels of depurination of the reaction product as explicitly taught by Greene et al (page 106). In addition, it would have been obvious to the ordinary artisan that the known technique of using the purging fluid density of Greene et al could have been applied to the method of Gamble et al in view of Anderson et al, Bass et al, and Schleifer et al with predictable results because the purging fluid density of Greene et al predictably results in reliable purging of the array.

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9. Claim 45 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gamble et al (U.S. Patent No. 5,981,733, issued 9 November 1999) in view of Anderson et al (U.S. Patent No 5,186,824, issued 16 February 1993) in view of Bass et al (U.S. Patent Application Publication No. US 2003/0003222 A1, published 2 January 2003) in view of Schleifer et al (U.S. Patent No. 6,309,828, issued 30 October 2001) as applied to claim 28 above, and further in view of Mian et al (U.S. Patent No. 6,319,469, issued 20 November 2001).

Regarding claim 45, the method of claim 28 is discussed above in Section 7.

While neither Gamble et al, Anderson et al, Bass et al, nor Schleifer et al explicitly teach specific flow rates, Anderson et al do teach the method wherein the flow rate is controlled and monitored during passage of reagents (column 5, lines 25-27 and column 14, lines 44-53 21). Anderson et al further teach that it is advantageous to control the flow rate because some synthesis steps take more or less time than other steps and because reagent waste resulting from excess use of reagents is expensive (column 21, lines 30-65). Thus, the reference clearly suggests that the flow rate is adjusted to maximize reagents and synthetic step.

In addition, Mian et al teach a method of synthesizing oligonucleotides on a disc (Figure 23b and column 5, lines 65-67), wherein the flow rates are from about 1 cm/sec to about 20 cm/sec having the added advantage that variable flow rates within the claimed range allow fluid transfer over a wide range of times scales as required by the various processes (column 12, lines 40-57). Thus, Mian et al teach the known technique of using the instantly claimed flow rates.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the flow rates of the method of Gamble et al in view of Anderson et al, Bass et al, and Schleifer et al with the range of flow rates as taught by Mian et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method of producing an addressable array having the added advantage of having flow rates that allow fluid transfer over a wide range of times scales as required by the various processes as explicitly taught by Mian et al (column 12, lines 40-57). In addition, it would have been obvious to the ordinary artisan that the known technique of using the range of flow rates as taught by Mian et al could have been applied to the method of Gamble et al in view of Anderson et al, Bass et al, and Schleifer et al with predictable results because the range of flow rates as taught by Mian et al predictably results in flow rates suitable for the synthesis of oligonucleotides on an array.

10. Claim 53 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gamble et al (U.S. Patent No. 5,981,733, issued 9 November 1999) in view of Anderson et al (U.S. Patent No 5,186,824, issued 16 February 1993) in view of Bass et al (U.S. Patent Application Publication No. US 2003/0003222 A1, published 2 January 2003) in view of Schleifer et al (U.S. Patent No. 6,309,828, issued 30 October 2001) as applied to claim 28 above, and further in view of Farr (U.S. Patent No. 3,969,250, issued 13 July 1976).

Regarding claim 53, the method of claim 28 is discussed above in Section 7.

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Neither Gamble et al, Anderson et al, Bass et al, nor Schleifer et al teach a pressure gradient.

However, Farr teaches stratification of liquids using a pressure gradient; namely, creation of supernatant fluid by centrifuging immiscible liquids (column 1, lines 5-10), which is in accordance with the statement on 33 of the instant specification that centrifugal acceleration is used to generate pressure gradients. Farr also teaches the stratification created by the pressure gradient has the added advantage of eliminating the need for decanting, thereby minimizing labor and possible contamination of the sample (column 2, lines 24-26). Thus, Farr teaches the known technique of using a pressure gradient.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising using a stratified interface as taught by Gamble et al in view of Anderson et al, Bass et al, and Schleifer et al so that the stratified interface is achieved using a pressure gradient as taught by Farr to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method of producing an addressable array having the added advantage of minimizing labor and possible contamination of the sample as explicitly taught by Farr (column 2, lines 24-26). In addition, it would have been obvious to the ordinary artisan that the known technique of using the pressure gradient of Farr could have been applied to the method of Gamble et al in view of Anderson et al, Bass et al, and Schleifer et al with predictable results

because the pressure gradient of Farr predictably results in reliable method of stratifying fluids.

Response to Arguments

11. It is noted that Applicant's arguments filed 9 January 2009 (hereafter the "Remarks") are identical to the after-final arguments filed 11 December 2008, except for the paragraph on page 7 of the Remarks regarding the non-compliant after-final amendment. The after-final arguments were previously responded to in the Advisory Action mailed 29 December 2008.

While the rejections presented above are new ground(s) of rejection necessitated by the amendments, the responses to Applicant's arguments previously presented in the Advisory Action that are relevant to the instant rejections are reiterated below. Thus, the responses below are a complete response to the instant Remarks.

A. Applicant argues on page 9 of the Remarks that Gamble does not teach wash reagents contacting the entire surface of the substrate. Thus, Applicant is attacking the individual reference of Gamble et al.

However, as noted in the previous Final Office Action, Gamble et al merely lack the teaching that the wash solution flows through the same chamber even though Gamble et al explicitly teach the substrate is placed in a reaction chamber wherein reagents flow over and immerse the substrate (column 3, line 45-column 4, line 5), and that the reagents include phosphoramidites (i.e., blocked nucleoside monomers), wash

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reagents, deprotection (i.e. deblocking) reagents, activation reagents, oxidation reagents, and any other necessary synthesis reagents (column 4, lines 35-46).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

B. Applicant argues on page 9 of the Remarks that Anderson et al do not teach in situ fabrication of an array. Thus, Applicant is attacking the individual reference of Gamble et al.

However, as noted in the previous Final Office Action, Anderson et al is not relied upon for the teaching of the formation of an in situ array. Anderson et al clearly teach in situ synthesis of oligonucleotides on a substrate, and further teach the forming of a liquid-liquid interface such that the solid support is not exposed to a triple phase interface (column 12, lines 28-67 and Fig. 2A-2D), as well as teaching the use of a single hollow chamber as a reaction chamber has the added advantage of allowing precise control of fluid flow and minimization of both micro-and macro-anomalous flow (Abstract).

In response to applicant's arguments against the references individually, it is reiterated that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references.

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C. Applicant argues on page 10 of the Remarks that because the prior art of Gamble et al and Anderson et al are "very different methods," there is no motivation to combine the references.

In response to applicant's argument that the cited references are "very different methods" (i.e., nonanalogous art), it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, Gamble et al teach a method of in situ forming of an oligonucleotide array using a flow of reagents through a flow chamber as described in the previous Final Office Action. Anderson et al teach known technique of performing all of the fluid steps, including washing, with a single reaction chamber during an in situ synthesis of oligonucleotides on a solid support as described in the previous Final Office Action. Thus, the methods bear a striking similarity, and are not, as Applicant asserts, "very different methods."

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Anderson et al

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also teach the use of a single hollow chamber as a reaction chamber has the added advantage of allowing precise control of fluid flow and minimization of both micro-and macro-anomalous flow (Abstract). Thus, Anderson et al teach the known technique of performing all of the fluid steps, including washing, with a single reaction chamber.

Thus, as clearly stated in the previous Final Office Action, it would have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising steps including washing of the array substrate as taught by Gamble et al so that each previous reagent is quantitatively replaced by a washing fluid as taught by Anderson et al and so that the reaction chamber of Gamble et al is used as a single reaction chamber for all of the fluid manipulation steps as taught by Anderson et al arrive at the instantly claimed method with a reasonable expectation of success. Quantitative replacement of reagents on the surface of the support requires displacement of said reagent from the entire surface of the substrate via use of the washing fluid as taught by Anderson et al. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method having the added advantage of ensuring that each reagent reacts properly so that the yield of the polymer is not diminished, thus meeting the fixed requirements of washing efficiency and quantitative replacement of solutions during polymer synthesis as explicitly taught by Anderson et al (column 19, lines 25-40 and column 3, lines 45-60). The ordinary artisan would also have been motivated to use the single reaction chamber of Anderson et al as a single reaction chamber for all of the fluid steps in the method of Gamble et al because the use of a single reaction

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chamber for all of the fluid steps, including washing, would have resulted in a method having the additional added advantage of allowing precise control of fluid flow and minimization of both micro-and macro-anomalous flow as explicitly taught by Anderson et al (Abstract). In addition, it would have been obvious to a person of ordinary skill in that art at the time the claimed invention was made that the known technique of performing all of the fluid steps, including washing, with a single reaction chamber as taught by Anderson et al could have been applied to the method of Gamble et al with predictably results because the known technique of performing all of the fluid steps, including washing, with a single reaction chamber as taught by Anderson et al predictably results in a reliable method of performing DNA synthesis steps.

In addition, it is also noted that under the Supreme Court ruling for *KSR Int'l Co. v. Teleflex, Inc* (No 04-1350 (US 30 April 2007) forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. See *Ex parte Smith* (USPQ2d, slip op. at 20 (Bd. Pat. App. & Interf. June 25, 2007)).

D. Applicant argues on page 10 of the Remarks that Anderson et al requires a rotor, which results in a nonfunctional embodiment, and would damage the array and render in situ fabrication impossible.

However, Applicant has not provided any evidence of inoperability. As such, the argument is deemed unsupported arguments of counsel. MPEP 716.01(c) makes clear that "[t]he arguments of counsel cannot take the place of evidence in the record" (*In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965)).

In addition, the teaching of Anderson is not limited to rotor/centrifuge, but also includes a "column at rest" (Abstract and Column 5, lines 29-30). Hence, the combination of Gamble et al and Anderson et al would not lead to a damaged substrate as asserted by Applicant.

E. Applicant also argues on pages 10-11 of the Remarks that there is no support that the combination results in washing efficiency or quantitative replacement of reagents.

However, as noted in the previous Final Office Action, Anderson et al teach the desire for washing efficiency and quantitative replacement of reagents, Anderson et al also teach the use of a single hollow chamber as a reaction chamber has the added advantage of allowing precise control of fluid flow and minimization of both micro-and macro-anomalous flow (Abstract). Thus, the control of both micro-and macro-anomalous flow would increase the washing efficiency because poor flow (i.e., low washing efficiency) would be minimized via the flow control.

In addition, it is reiterated that under the Supreme Court ruling for KSR Int'l Co. v. Teleflex, Inc (No 04-1350 (US 30 April 2007) forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness.

F. Applicant also argues on page 11 of the Remarks that Gamble et al teach drying protocols in column 13.

However, column 14 clearly states that "other versions" of the claimed invention "are possible" and column 3 of Gamble et al clearly states that anhydrous conditions in the chamber "can be accomplished" by drying. Thus, the drying protocols are non-

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limiting, and Gamble et al clearly allow for other methods of guaranteeing reagent removal.

G. Applicant argues on pages 11-12 of the Remarks that numerous other teachings around to priority dates teach the prevalence of drying steps and lack the teaching of fluid displacement.

However, the presence of other references that do not teach fluid displacement does not negate the fact that the prior art of Anderson et al teaches the known technique fluid displacement in a single chamber as well as a motivation to do so as provided in the previous rejections.

H. Applicant argues on pages 12-13 that the combination of Gamble et al and Anderson et al results in an inoperable embodiment because of the alleged need for a rotating rotor and the lacking of an addressable array in Anderson et al.

However, as noted above, Applicant has not provided any evidence of inoperability. As such, the argument is deemed unsupported arguments of counsel. MPEP 716.01(c) makes clear that "[t]he arguments of counsel cannot take the place of evidence in the record."

Further, as also noted above, the teaching of Anderson is not limited to rotor/centrifuge, but also includes a "column at rest" (Abstract and Column 5, lines 29-30). Hence, the combination of Gamble et al and Anderson et al would not lead to a damaged substrate as asserted by Applicant.

It is also reiterated that Applicant's arguments amount to a piecemeal analysis of the references. In response to applicant's arguments against the references individually,

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it is reiterated that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references.

I. Applicant also argues on page 13 of the Remarks that the "Examiner has fails [sic] to articulate a reason to modify the cited references...[w]ithout hindsight provided by the instant application...."

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

J. Applicant's arguments on pages 13-14 of the Remarks regarding the rejection of claim 37 rely on the alleged deficiencies of Gamble et al in view of Anderson et al. These arguments are addressed above. Because the arguments regarding alleged deficiencies of Gamble et al in view of Anderson et al were not persuasive, the claim remains rejection for the reasons presented above.

K. Applicant argues on pages 14-15 of the Remarks that because Mian et al teaches channel flow in a disc, the art of Mian et al cannot be combined with Gamble et al or Anderson et al (i.e., that Mian et al is non-analogous art).

However, Gamble et al clearly teach fluid flow through channels 160 (Figure 11) and a conduit system for transporting liquids to and from the reaction chamber (column 4). Mian et al teach the advantage that variable flow rates within the claimed range allow fluid transfer over a wide range of times scales as required by the various processes (column 12, lines 40-57). Thus, Mian et al teach the known technique of using the instantly claimed flow rates and the ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method of producing an addressable array having the added advantage of having flow rates that allow fluid transfer over a wide range of times scales as required by the various processes as explicitly taught by Mian et al (column 12, lines 40-57).

L. Applicant argues on pages 14-15 of the Remarks that Gamble et al and Bass et al lack the stratified fluid interface. Thus, Applicant poses a piecemeal analysis of the rejection by not addressing the stratified fluid interface taught by Anderson et al.

It is reiterated that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references.

M. Applicant argues on page 15 of the Remarks that because Anderson et al teaches a rotating rotor, there can be no teaching of the use of the flow cell of Bass et al.

However, as noted above, Anderson is not limited to rotor/centrifuge, but also includes a "column at rest" (Abstract and Column 5, lines 29-30). Thus, a column at rest is a functional equivalent of the claimed "flow cell," and the use of the functionally

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equivalent flow cell of Bass et al is an obvious substitution for the reasons presented in the rejection.

N. Applicant argues on page 16 of the Remarks that Farr teaches a stratified blood supernatant and thus is unrelated to array synthesis; i.e., that Farr is non-analogous art.

In response to applicant's argument that Farr is nonanalogous art, it is reiterated that it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, Farr refers to manipulation of stratified fluids using a pressure gradient (column 1, lines 5-10). Anderson et al also teach stratified fluids (column 12, lines 28-67 and Fig. 2A-2D). Thus, Farr is analogous to Anderson et al.

O. Applicant also argues on page 16 of the Remarks that the examiner has misconstrued the advantage taught by Farr.

However, as noted above, the Supreme Court ruling for *KSR Int'l Co. v. Teleflex, Inc* (No 04-1350 (US 30 April 2007) forecloses the argument that a specific teaching, suggestion, or motivation is required to support a finding of obviousness. Thus, it would have been obvious to the ordinary artisan that the known technique of using the pressure gradient of Farr could have been applied to the method of Gamble et al in view of Anderson et al with predictable results because the pressure gradient of Farr

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predictably results in reliable method of stratifying fluids, as stated in the previous Final Office Action.

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert T. Crow whose telephone number is (571)272-1113. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert T. Crow/
Examiner, Art Unit 1634

Robert T. Crow
Examiner
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